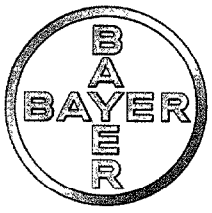
Bayer HealthCare



January 15, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane Room 1061
Rockville, MD 20852

Re: Docket No. 2003D-0497; Industry Comments
Draft Guidance for Industry on Pharmacogenomic Data Submissions

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This letter is to provide comments to the above-referenced Draft Guidance from Bayer HealthCare LLC. Bayer appreciates the opportunity to provide comments in an effort to continue the dialogue with stakeholders regarding the submission of pharmacogenomics data.

Bayer comments from the diagnostics perspective are as follows:

1. Well-established performance characteristics

   It would be helpful if FDA could clarify its expectations for what criteria, and with what objective evidence, a pharmacogenomic test would be considered to have "well-established performance characteristics" for use as a valid biomarker. There might be several mechanisms available to a diagnostics company to provide this assurance, e.g., through an IDE filed with FDA that could be cross-referenced by a pharmaceutical company, an approved PMA preclinical module that establishes performance characteristics, or perhaps a test could be established as a valid biomarker through an IVAT-type of FDA clearance mechanism. Would an in-house validated test, such as a homebrew, qualify as a test with "well-established performance characteristics"? There should be some established standard for what constitutes "well-established performance characteristics" for purposes of a valid biomarker and for assuring the test data can be effectively used in a drug submission.

2. Test platform

   It would be helpful if FDA could comment on its understanding of the relative importance of the test platform on whether a test is considered a valid biomarker, i.e., is a valid biomarker specific to a

particular platform? For example, if a panel of markers has been called a valid biomarker based on the results of expression analysis on an Affymetrix chip would it still be a valid biomarker if you measured the panel of markers using a Luminex or TaqMan platform? Would FDA consider equivalence testing sufficient to qualify a test on a different platform as a valid biomarker, or would FDA require retrospective or prospective clinical studies? There should be an established standard and/or expectations for how to change to another testing platform while keeping the designation of known or probable valid biomarker. The platform issue is of particular concern since it has been recognized that genomic data can "yield different answers when different analytical and bioinformatics methods are used" (taken from Salerno and Lesko 2004 *Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal*, Pharmacogenomics **5**(1), 25-30.)

3. "Known valid biomarker" and clinical utility

   Is it reasonable to expect that if a test is considered a "known valid biomarker" it could also be considered to have clinical utility for purposes of IVD approval, i.e., would it be necessary to conduct additional studies to establish clinical utility in a premarketing application for a test that is a "known valid biomarker"?

4. "Known" versus "probable" valid biomarker

   It is not clear if there is added value of a test being considered a "known valid biomarker" as compared to a "probable valid biomarker" for either obtaining drug approval or premarket clearance for the test. There might be more incentive for a diagnostic or pharmaceutical company to invest in elevating the test from "probable" to "known" if there is a clear advantage to the distinction. It would also be helpful if FDA could clarify its expectations for how a test might move from "probable" to "known" status. For example, does premarket clearance or approval automatically place a test in the "known" category? There should be clear expectations and a formal mechanism for how a test moves from one category to the other, particularly if there is added value to either the drug or test approval process.

5. Gold Standard

   Mutations in some of the P450 enzymes have been indicated as "valid biomarkers". However there is no FDA approved test for these mutations. In many cases the mutations are determined by

sequencing. If sequencing is used more often does it automatically become the de facto gold standard? Would there be an additional requirement to establish equivalence to sequencing if a drug study utilized P450 genotyping as part of a drug submission?

Additional Bayer comments from the pharmaceutical perspective are as follows:

1. Voluntary Submission Process

   FDA has requested that exploratory pharmacogenomics data be submitted in a VGDS so that the Agency can "analyze the data" and "verify results". If known, it would be informative if FDA could specify further what that process will be. In addition, if FDA is able to "verify results", particularly those from human clinical trials, does this then serve to categorize the data (e.g. gene expression profile) as either a " known valid biomarker" or "probable valid biomarker"? Similarly, would publication in a peer-reviewed scientific journal serve this purpose? If not, and especially in the case of a "known" biomarker, what else would be required since "widespread agreement in the medical or scientific community" will be difficult, or even nearly impossible, when a proprietary compound or drug is the test agent?

Sincerely,

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